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SCIENTIFIC CONSULTANTS to INDUSTRY and COUNSEL

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May 27, 2005

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

Re: Docket No. 77N-0094
Aspirin for Primary Prevention of Myocardial Infarction
Thrombosis Prevention Trial – Additional Analysis of Silent MI

Dear Sirs,

Reference is made to Bayer HealthCare's Citizen Petition submitted on February 11, 2003 seeking approval for the use of aspirin in individuals at moderate risk or greater of coronary heart disease (CHD) who have not experienced a previous MI. The basis of the Petition was information from 5 adequate and well-controlled clinical trials, involving over 55,000 apparently healthy subjects, demonstrating the benefits of low dose aspirin (75-325 mg) in reducing the risk of MI (32%).

Reference is also made to the December 8, 2004 Cardiovascular & Renal Drugs Advisory Committee meeting, during which the FDA presented information from the Thrombosis Prevention Trial (TPT). The TPT trial included patients deemed to be at moderate risk (>10%) and demonstrated non-fatal MI risk reductions equivalent to the other four primary prevention studies (32%). It appears that the FDA statistical reviewer included silent MIs from the TPT and suggested that no effect on MI was achieved. Based on the *post-hoc* nature of these analyses, the evaluation was not considered appropriate. Following the FDA's presentation a decision was made to further analyze the silent MIs that were recorded during the study. This analysis conducted by Dr. Thomas Meade and his colleagues is attached.

If you have any questions regarding the attached information, please contact Dr. Steven Weisman at 973-889-1600 (x 101).

Sincerely,

Joanne Robinett
Director, Regulatory Affairs

77N-0094 SUP 55

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**Silent myocardial infarction (MI) in the Medical Research Council's Thrombosis Prevention Trial**

## Introduction

Routine 12-lead electrocardiograms (ECGs) were carried out on all participants in the Thrombosis Prevention Trial (TPT) at entry and at each annual medical examination. The number of annual visits and therefore of repeat ECGs did of course vary considerably between participants according to whether they had had major terminating events (TEs), i.e. coronary death and fatal or non-fatal MI, or had withdrawn from randomised treatment. The median frequency of visits was 5, varying from 1 (for 535 men) to 13 (for 7 men). The research nurses in the 108 participating general practices were instructed in the procedure for obtaining satisfactory ECG tracings according to standard criteria (e.g. correct siting of leads). The tracings were checked by the trial's lead general practitioner in the practice concerned.

The ECGs were then sent to the coordinating centre and coded by two trained, independent readers. Any discrepancies were referred to a third reader for final resolution. The tracings were coded according to the Minnesota code, any of $1_1$, $1_2$, $1_3$ and $7_1$ being taken as evidence of silent myocardial infarction (MI). Each of the main Minnesota codes of Q and QS patterns, i.e. $1_1$, $1_2$ and $1_3$ are also given a third subscript so that, for example, $1_2$ may go up to $1_{2,8}$. (The paper with the main results, Lancet 1998, 351, 231-241, was confined to $1_1$ and $1_2$ as well as $7_1$ However, it is clear that most if not all $1_3$ sub-groups definitely or very probably represent silent MIs as well. Their inclusion increases the power for the analyses in Tables 7 and 8.)

**Results**

Table 1 shows that 272 men (5.0%) had had silent MIs at entry to the trial. Of the 272 men, 257 were recorded with either code $1_1$, $1_2$ or $1_3$; whilst 15 men were coded as $7_1$.

**Table 1. Numbers (N) and percent (%) of men with codes for silent MI at entry to the trial.**

| Silent MI | N | % |
|---|---|---|
| No | 5,227 | 95.05 |
| Yes | 272 | 4.95 |
| Total | 5,499 | 100.00 |

Table 2 shows that of the 23,006 annual examinations, $1_1$, $1_2$ or $1_3$ was recorded 1,517 times (6.6%). These recordings were found in 719 men (15.4% of the 4,661 men with annual examinations) on at least one occasion, inclusive of those with silent MIs at entry. Similar recordings were observed in the in 210 men (4.5%) with silent MI at entry among the 4,661 men with annual examinations.

**Table 2. Numbers (N) and percent (%) of annual examinations on which code 1 was recorded.**

| Code 1 | N | % |
|---|---|---|
| 1 | 190 | 0.83 |
| 2 | 518 | 2.25 |
| 3 | 809 | 3.52 |
| Sub-total | 1517 | 6.60 |
| None | 21,489 | 93.41 |
| Total | 23,006 | 100.00 |

Table 3 gives the number of times $1_1$, $1_2$ or $1_3$ was recorded according to the corresponding third digit sub-groups for each (so that sub-group 7 refers only to those with $1_1$ or $1_2$ and sub-group 8 refers only to $1_2$).

**Table 3. Numbers of third digit sub-groups in codes $1_1$, $1_2$ or $1_3$.**

| Code | Sub-groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| $1_1$ | 75 | 32 | 10 | 24 | 7 | 36 | 5 | . |
| $1_2$ | 40 | 43 | 30 | 70 | 12 | 215 | 34 | 74 |
| $1_3$ | 108 | 261 | 95 | 194 | 9 | 142 | . | . |

Table 4 shows the number of examinations on which code 7 was recorded, with sub-groups. On 101 occasions (3.9%) the code was $7_1$ and this was recorded in 45 individuals with this code on at least one occasion, inclusive of those with silent MIs at entry. Code $7_1$ was also recorded in 11 (among 4,661 men with annual examinations) individuals at entry.

**Table 4. Numbers (N) and percent (%) of times code 7 was recorded in each second digit sub-group.**

| Code 7 sub-groups | N | % |
|---|---|---|
| **1** | **101** | **3.89** |
| 2 | 378 | 14.55 |
| 3 | 882 | 33.96 |
| 4 | 96 | 3.70 |
| 5 | 984 | 37.89 |
| 6 | 156 | 6.01 |
| Total | 2,597 | 100.00 |

Table 5 shows the number of participants who had either code 1 or code 7 recorded (including those with silent MIs at entry) among the 4661 who had at least one follow-up after entry examination. Among the 809 men with either code, 233 (28.8%) did not have similar codes on subsequent annual examinations following a first occasion on which a code for silent MI was found.

**Table 5. Numbers (N) and percent (%) of times any code for silent MI was recorded.**

| Code for silent MI | N | % |
|---|---|---|
| No | 3,852 | 82.64 |
| Yes | 809 | 17.36 |
| Total | 4,661 | 100.00 |

Table 6 shows the numbers and percent of men in whom a silent MI was recorded on at least half of the subsequent annual examinations. Thus, about half the men with a recording for a first silent MI did not have one subsequently.

**Table 6. Consistency of recorded silent MIs**

| Numbers of annual exams after first recorded silent MI | No. of men | No. of men (and %) in whom silent MI recorded on at least half the subsequent annual examinations |
|---|---|---|
| 0 | 145 | - |
| 1 | 114 | 54 (47.4) |
| 2 | 104 | 65 (62.5) |
| 3 | 111 | 59 (53.2) |
| 4 | 106 | 57 (53.8) |
| 5 | 86 | 49 (57.0) |
| 6 | 61 | 31 (50.8) |
| 7 | 29 | 20 (69.0) |
| 8 | 18 | 8 (44.4) |
| 9 | 6 | 4 (66.7) |
| 10 | 3 | 3 (100.0) |
| 11 | 2 | 2 (100.0) |

Table 7 gives the numbers of men with an initial recording for silent MI who subsequently experienced a major clinical event. Of the 809 with an initial recording of silent MI (at entry or subsequent annual examination), 99 (12.2%) later experienced a major event. A total of 225 men (5.8%) of the 3,852 who did not have a silent MI later went on to have a major event. The difference between those with or without a silent MI recording (5.8% compared with 12.2%) is significant ($p<0.0001$). The crude hazard ratio for having a major event after a silent MI recording was 2.10 (95%CI 1.67, 2.62) and 2.38 (95% CI from 1.86 to 3.04) after adjustment for active treatment.

**Table 7. Numbers of men with recordings for silent MI who subsequently experienced a major clinical event, i.e. coronary death or fatal or non-fatal MI.**

| Silent MI | Subsequent event | | Total | HR (95% CI) | p-value |
|---|---|---|---|---|---|
| | No | Yes | | | |
| No | 3,627 | 225 | 3,852 | 1.0 | - |
| Yes | 710 | 99 | 809 | 2.38 (1.86, 3.04)[1] | <0.0001 |
| Total | 4,337 | 324 | 4,661 | | |

[1] **adjusted for treatment**

Table 8 shows, first, the number of men in the three defined groups who did not have a silent MI recorded at entry but who later had a recording for silent MI. However, it should of course be recognised that, as a result of the variability of silent MI referred to earlier, some participants without a recording at entry might have had one prior to entry. Secondly, table 8 shows the hazard ratios (HR) and 95% confidence intervals (95% CI) for the comparison of aspirin with placebo on the occurrence of silent MI. A silent MI was recorded on at least one annual examination in 267/2078 (12.8%) men randomised to aspirin compared with 288/2122 (13.6%) in men randomised to placebo aspirin. Table 8 shows the results of this comparison between aspirin and placebo for three different

ways of classifying the presence of silent MI. None of the HRs are significant, indicating that aspirin does not appear to modify the onset of silent MI.

**Table 8. Hazard ratios (HR) and 95% confidence intervals (95% CI) of silent MI in those on active aspirin compared with placebo aspirin.**

| Coding of silent MI | Number of silent MI | | | HR | 95% CI |
|---|---|---|---|---|---|
| | Overall | Active Aspirin | Placebo Aspirin | | |
| Silent MI ever recorded | 555 | 267 | 288 | 0.95 | 0.81 to 1.13 |
| Silent MIs recorded $\geq$ once after first recording | 233 | 110 | 123 | 0.94 | 0.73 to 1.21 |
| Silent MI on approx. half visits after first recording | 155 | 73 | 82 | 0.92 | 0.67 to 1.26 |

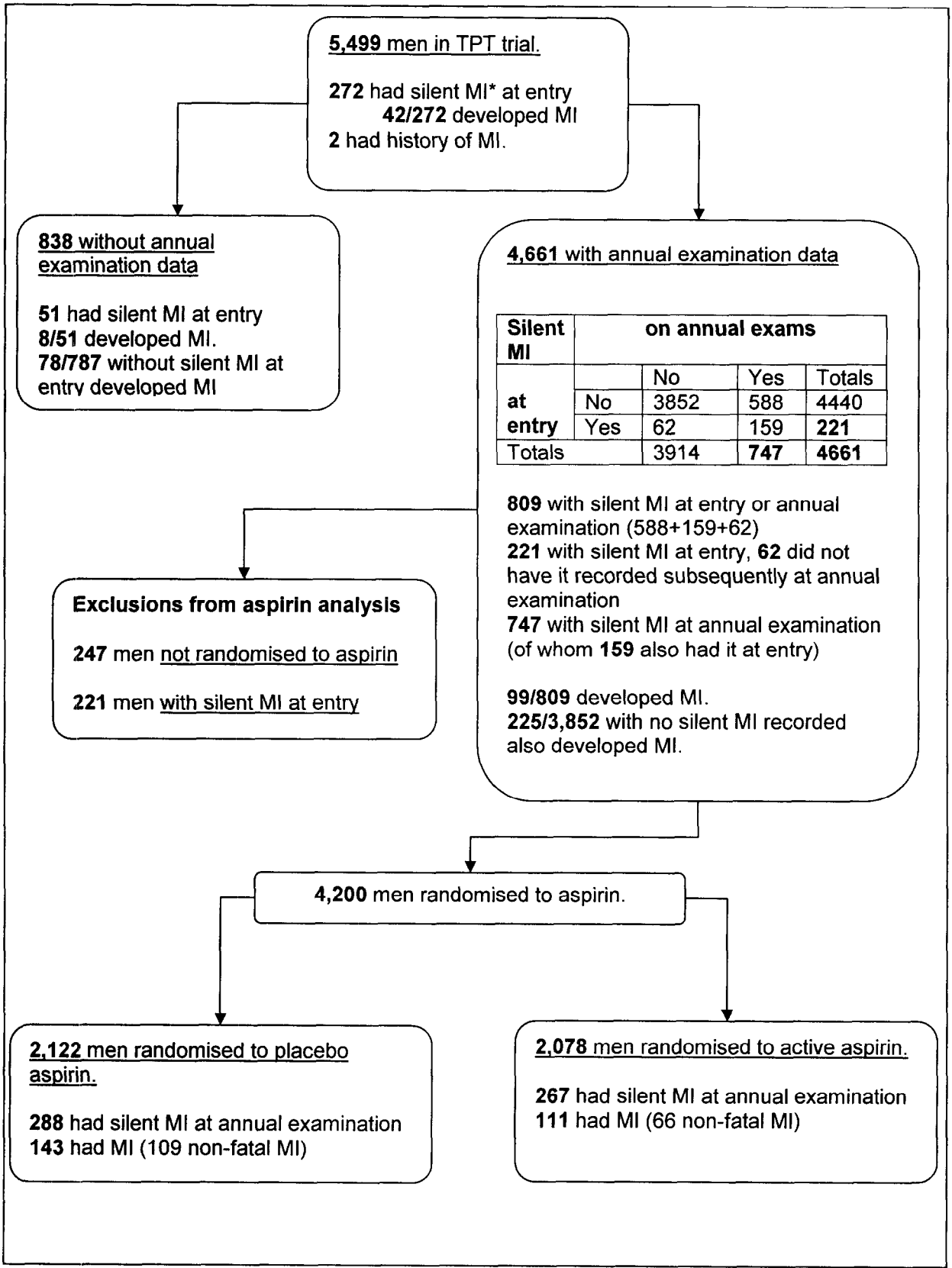
**Main conclusions**

(i) Among individual men, there is considerable variability in the finding of a silent MI. These are often not recorded consistently after an initial recording.

(ii) The data confirm that the finding of a silent MI significantly increases the risk of a major clinical event subsequently.

(iii) Aspirin does not appear to have an effect on the onset of silent MI.

26 May 2005




*Silent MI code $1_1$ $1_2$ $1_3$ and $7_1$